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NICOTINE, RESORPTION AND FATE

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1. INTRODUCTION

In 1876, Lautenbach observed that the toxic effects of nicotine, administered to a dog, were reduced following passage through the liver. These experiments probably represent the first scientific investigation of nicotine pharmacology, toxicity, distribution and metabolism in the sense that we understand these terms today. However, it was some considerable time before Werle and Uschold (1948) described the detoxification of nicotine by the guinea-pig liver *in vitro* and this report seems to represent a reawakening of interest in the metabolism of the compound, which is one of the most widely used drugs in human society, and coincides with the beginning of the detailed biochemical investigation of drug metabolism in mammals. These first experiments used rather crude methods whereas in more recent years the use of compounds labelled with radioactive isotopes has resulted in considerable progress in the field. In particular, Larson and his group, (Larson and Silvette, 1968), have used radiochemical methods with outstanding success in evaluating nicotine metabolism in the mammalian body and this can be thought of as the third period of research into nicotine metabolism.

It is important to realise that most of these experiments were performed before the impact of the statistical–epidemiological connection between certain diseases and tobacco smoking had made its full impact upon the scientific community, and we can only speculate on the reasons which encouraged these early authors to investigate nicotine metabolism. Presumably it was simply their professional curiosity as the study of the metabolism of foreign compounds became more interesting.

The statistical correlation between cigarette smoking and the spread of bronchial carcinoma in the population (Wynder, 1952) led to a steadily growing interest in the mechanism of this phenomenon, and the publication of the Terry Report (1964) released an avalanche of activity both in basic and epidemiological research promoted, to a large extent, by a substantial increase in the funds available for this type of research. Thousands of publications have appeared since that time, although perhaps to the surprise of many pharmacologists and biochemists, the early results of the scientists mentioned above have, to a large extent, remained undisputed and have certainly not been discarded. Of course, other results, including many important details, have been added to these early results on which we still rely.

In this paper, the present state of knowledge of the metabolic fate of nicotine will be reviewed in detail. This compound, which pharmacologically, is the most active constituent of tobacco smoke, is, in the opinion of this author, the main reason for the tobacco smoking habit. However, most species of tobacco plant contain alkaloids in addition to nicotine (e.g. nornicotine, anabasine, myosmine and nicotyrine) and these may all contribute to the taste and pharmacological actions of tobacco smoke. However, examination of their potential for pharmacological activity reveals that they are much less active than nicotine (Clark *et al.* 1965; Schievelbein, 1962; Werle and Schievelbein, 1961, 1962). In preparing this review, the author has attempted to restrict himself to results which are pertinent to the action of nicotine in the human organism receiving doses of the drug similar to those found in smokers. This is not always possible however, since results from human studies are very limited and, therefore, results from studies in experimental ani-

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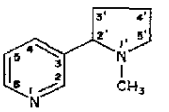

FIG. 1. Nicotine.

mals have also been considered. It is also important to remember that the dose of nicotine, received by a human smoker, varies a great deal and depends to a large extent on smoking behavior in each individual.

2. CHEMICAL PROPERTIES OF NICOTINE

The structure of nicotine [1-methyl-2-(3-pyridyl-pyrrolidine; $C_{10}H_{14}N_2$] was first proposed by Pinner and Wolfenstein (1892) and confirmed by Pictet (1895) by synthesis (Fig. 1). In the pure state, the compound is a clear liquid with a characteristic odour. It is miscible with an equal volume of water but partitions preferentially into organic solvents and can therefore be extracted from aqueous solution by solvent extraction. It is a strong base with a boiling point of 274.5°C at 760 torr although it can be distilled from mixtures or biological fluids relatively easily under reduced pressure. Further details of the chemical and physico-chemical properties of nicotine and the other alkaloids of tobacco have been reviewed previously (Schievelbein, 1961, 1962).

3. METHODS FOR THE ESTIMATION OF NICOTINE IN BIOLOGICAL FLUIDS

Most of the experiments, described in this review, especially those which include the measurement of nicotine concentrations in human blood and urine samples, have been made possible by the development of chemical methods for the quantitative estimation of nicotine in small concentrations. Earlier experiments had to rely on the classical bioassay systems for the compound such as blood pressure measurements in cats, dogs and rats, measurements of its effects on the isolated guinea-pig ileum and the reaction of the nictitating membrane of the cat eye.

Werle and Becker (1942) described a method which involved steam distillation of nicotine, from mixtures containing the material, followed by photometric estimation using the Koenig reaction with aniline and bromocyan. The Koenig reaction was used widely in the earliest experiments but it is not very specific since many pyridine compounds will give a positive reaction. Better specificity was obtained with the introduction of UV spectrometry which allowed nicotine to be measured using its absorption peak at 266 nm. This method, however, also lacked sensitivity.

Independently, Beckett and Triggs (1966) and Schievelbein and Grundke (1968) developed methods for the estimation of nicotine by gas liquid chromatography. This method has been modified and partly improved by other workers (Feyerabend and Russell, 1979; Hengen and Hengen, 1978) who have reported that the plasma nicotine level, measured 20 min after smoking one cigarette, lies between 20 and 70 ng/ml, a range which is now generally accepted to be accurate. In recent years, the method has been used to measure plasma nicotine and to estimate the levels of nicotine, cotinine and nicotine-1′-*N*-oxide in urine.

A radioimmunoassay for nicotine and cotine has been developed by Van Vunakis (1974). However, the method depends upon the preparation of suitable antigens and antibodies which are not available commercially. Methods involving the combination of gas liquid chromatography and mass spectrometry are able to detect minute quantities of nicotine although the practicability of these techniques seems to be limited by the high nicotine contamination levels found in the ambient air of nearly every laboratory working with nicotine (Horning, 1974) or by smoking in the vicinity.

A complex method for the estimation of nicotine in humans has been developed by Maziere *et al.* (1979). It involves the synthesis of ^{11}C-labelled nicotine by the introduction

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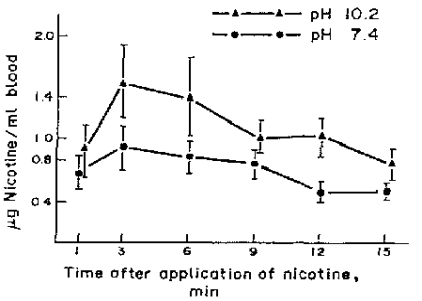

FIG. 2. Blood levels of nicotine after oral applications; means (±S.D.). For details see text.

of $^{11}CH_3$ into nornicotine. The labelled nicotine so produced has a short half-life. However, the method is expensive, requiring a cyclotron to produce the radioisotope.

4. ABSORPTION

The effect of pH on the absorption of a drug through artificial and biological membranes can be predicted from the Henderson–Hasselbalch equation. Thus the rate of absorption of nicotine should be increased as the nicotine solution becomes more alkaline and the proportion of the drug in the nonionized form increases. Tobacco smoke can be regarded as an aerosol in which nicotine is suspended within the aqueous fraction. The rate of absorption through biological membranes should therefore increase as the pH of this aqueous fraction increases. The results of these theoretical considerations can be demonstrated by experiment as will be seen in the next section.

4.1. Absorption from the Oral Cavity

The absorption of nicotine through the oral mucosa is the principal route of absorption for cigarette and cigar smokers who do not inhale and for snuff users. Schievelbein *et al.* (1973a,b) have examined the effect of pH on the absorption of nicotine administration as a spray directed into the oral cavity of dogs anesthetized with Nembutal® and in whom the trachea and esophagus had been tied in the cervical region. The results of these studies showed that nicotine absorption, measured both directly as the concentration of the alkaloid in the plasma and indirectly as increased blood pressure, increased as more alkaline solutions of the drug were used in the spray (Fig. 2). The data therefore confirmed the predictions of the Henderson–Hasselbalch equation as they apply to nicotine.

The pH of the aqueous fraction of cigar smoke is generally around 8.5, and measurements made by Russell and his colleagues (Russell *et al.*, 1980) have shown that the absorption of nicotine in a noninhaling subject smoking a cigar slowly rises to give a plasma level of 20 ng/ml after 70 min (Fig. 3). In this experiment the authors compared blood nicotine levels in a noninhaling cigar smoker, an inhaling cigarette smoker and a subject using a nicotine-containing chewing gum. The results of the study (Fig. 3) showed

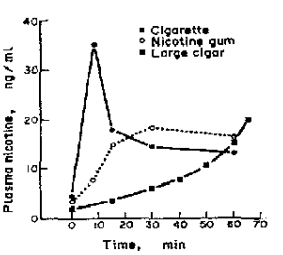

FIG. 3. Blood nicotine concentration after chewing one piece of 4 mg gum compared with smoking a cigarette (1–2 mg nicotine) and a large Havana cigar. At least 12 hr abstinence before testing (Russell *et al.*, 1980).

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TABLE 1. *Mean Nicotine (ng/ml) Contents in Blood of Dogs after 1 Puff (45 ml) of Smoke of Different Brands of Cigarettes*

Type of cigarette	Time (sec)					Nicotine contents of smoke (mg)
	Immediately after puff	15	30	45	60	
Virginia	60	62	39	23	15	1.9
'Black' type	23	24	13	5	5	1.44
German blend	23	26	15	8	0	0.52

$n = 6$; artificial respiration.

that the amounts of nicotine absorped from the three sources were comparable after approximately 70 min. This observation may be of particular significance in view of the recent introduction of nicotine-containing chewing gum as a palliative during smoking withdrawal.

4.2. Absorption through the Skin

Nicotine can be absorped through the skin although this is only of clinical significance for 'tobacco croppers' and people who use nicotine as an insecticide who may become acutely poisoned with the alkaloid as a result of percutaneous absorption (Schievelbein, 1972; Weizenecker and Deal, 1970).

4.3. Absorption through the Lungs

The data presented in Table 1 show that the absorption of nicotine through the alveoli of lung seems to be related simply to the concentration of the alkaloid in the smoke, and that the influence of the pH of the aqueous phase of the smoke is negligible. These results were taken from studies in which smoke was blown into the lungs of anesthetized dogs by artificial respiration. However, the pH of the aqueous phase of cigarette smoke rarely exceeds 6.5 (only the smoke from the so-called 'black cigarettes' reaches a pH of between 7.3 and 7.5). These results are therefore consistent with the earlier observations of Armitage *et al.* (1974) who suggested that nicotine from cigarette smoke is poorly absorped through the buccal mucosa but rapidly absorped in the lungs. In support of this conclusion, Armitage (1974) has shown that, in two noninhaling human cigarette smokers, the peak plasma nicotine levels were 8.0 and 2.5 ng/ml in arterial blood whereas in four inhaling subjects the levels reached 30–40 ng/ml.

The rapid absorption of nicotine by the lungs has also been demonstrated pharmacoligically by Armitage (1974) who showed that the rapid increase in plasma nicotine levels was associated with an increase in arterial blood pressure and heart rate. An increase in the heart rate, from the resting pulse rate of 75/min, was observed as soon as the subjects began smoking, reaching a peak of 104 beats/min after 5 min. The systolic and diastolic blood pressure increased to a peak over approximately the same period of time. Thus it is clear that nicotine absorption from inhaled smoke is almost equivalent to an intra-arterial injection of the drug. More data on nicotine absorption from inhaled smoke is presented later in Section 6.

4.4. Nicotine Concentration in the Blood of Smokers

Schievelbein and Grundke (1968) found that the concentration of nicotine in the blood of smokers lay between 20 and 40 ng/ml. Russell *et al.* (1980) investigated the nicotine levels in 212 women and 151 men two minutes after smoking a cigarette and found them to be between 4 and 72 ng/ml. Also, estimations using a radioimmunoassay for nicotine

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(Haines *et al.*, 1974) showed that the mean concentration was 20.6 ng/ml one minute after cessation of smoking. No nicotine could be found in the blood 20 min after smoking.

4.5. Absorption from the Urinary Bladder

The absorption of nicotine from the urinary bladder seems to follow the same criteria as those which govern its absorption from the oral cavity since the pH of the urine greatly influences the rate of reabsorption of excreted nicotine. The movement of nicotine through the mucosa of the bladder is increased when the alkaloid is, for the most part, unionized (pH 9). No nicotine is reabsorped if the pH of the urine drops below 6 (Borzelleca, 1963). The dependence of nicotine reabsorption on urinary pH has subsequently been confirmed in humans by Feyerabend and Russell (1978). The reabsorption of nicotine from the urinary bladder may be of practical importance. Schachter (1978) discussed the possibility that smoking behavior may be influenced by the amount of nicotine reabsorped from the bladder since a fast rate of reabsorption could maintain the plasma nicotine levels at a high level for a longer period of time and thus the need to smoke could be diminished. He attempted to test the hypothesis *in vivo* by making the urine of his test subjects alternately acid and alkaline and trying to associate increased smoking with the increased nicotine excretion observed in the subjects with the acid urine. The experiments appeared to be successful although, as Schachter (1978) emphasizes, the results were only preliminary and obtained with only a few subjects.

4.6. Absorption from the Gastrointestinal Tract

The absorption of nicotine from the stomach seems to be poor, probably because of the acidic nature of the stomach juice. However, the only observations available are rather old, the most recent being those of Terasaka (1927) and Travell (1940).

4.7. The Mechanism of Nicotine Absorption and Associated Pharmacological Effects

The influence of the pH of the aqueous phase of smoke or of applied nicotine solutions on the absorption of the drug through biological membranes, such as those of the oral cavity and stomach, have already been discussed. There is no evidence known to this reviewer that nicotine can be actively transported across any biological membranes. The potent monoamine oxidase inhibitor, nialamide, has been shown to inhibit the liberation of biogenic amines evoked by nicotine (Schievelbein, 1963) although this effect is almost certainly the result of an effect of nialamide on nicotine absorption and not to the influence of this compound on the activity of the oxidase. All these observations lead to the conclusion that the only mechanism by which nicotine enters tissues is by a process of passive diffusion of the unionized compound across cell membranes. This opinion is supported by the results of the studies of Putney and Borzelleca (1971a,b) on the uptake of *N*-methyl-^{14}C-nicotine into rat submaxillary glands.

Nicotine has a potent depolarizing effect on membrane potentials particularly in the nervous system. (For detailed reviews of the evidence see Herz, 1968; Larson *et al.*, 1961, 1968, 1971, 1975; Rémond and Izard, 1979.) It seems very likely that the effects of nicotine in the central nervous system and the associated changes in behavior are related particularly to the depolarizing action of the drug.

Nicotine is known to cause the liberation of biogenic amines in the central nervous system (Schievelbein, 1967) and it seems reasonable to suggest that changes in the release of amines such as epinephrine, norepinephrine and acetylcholine (Armitage, 1975) may contribute to the arousal effect observed when a cigarette is smoked. The sedation, which is frequently observed after smoking, may be the result of the 5-hydroxytryptamine (serotonin) release which has been reported to occur from a number of tissues, including brain, following cigarette smoking (Schievelbein and Werle, 1962a). This conclusion is

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reinforced by the observations of Yoshida *et al.* (1970) who reported that the synaptosome fraction from brain tissue contains [illegible] cholinergic' receptors. Also the administration of nicotine directly into the [illegible] causes the release of norepinephrine (Hall and Turner, 1972), where [illegible] application to the spinal cord decreases 5-hydroxytryptamine turnover in that [illegible] The effects of nicotine on catecholamine release have been subsequently confirmed (Cry[illegible] *et al.*, 1976).

There are other factors, particularly the way in which the tobacco is smoked, which influence the absorption and pharmacological effects of nicotine. For example, there is a direct relationship between nicotine absorption and the degree to which a smoker inhales; depth of inhalation; the number and duration of puffs; the volume of each puff; the length of the cigarette or cigar butt; the force of drawing and last, but not least, the number of cigarettes smoked within a given unit of time. These factors, known collectively as *smoking behaviour*, are discussed extensively elsewhere (Dunn, 1973; Eysenck, 1965). This reviewer, however, is of the opinion that the main reason why an habitual smoker smokes is in order to experience the effects of nicotine in the central nervous system.

5. FATE

5.1. Distribution

The rapid elimination of nicotine from blood, observed by Schievelbein and Grundke (1968), has been confirmed by Turner (1969) and by Isaac and Rand (1969) who showed that it was also true when nicotine was administered in cigarette smoke and that the pattern of elimination was similar in dogs and man. Nicotine distributes between the plasma and blood cells of dogs in the ratio 1.0:0.8, an observation that has now also been shown to be true for human blood (Schievelbein, H., unpublished). In rats, pretreatment with ethanol lowers the plasma concentration of injected nicotine (Adir *et al.*, 1980). Leeds and Turner (1977) reported that, using equilibrium dialysis, very little nicotine is bound in the plasma of cats, pigeons or rats. However, Heuck *et al.* (1979) have shown that in human plasma, 80% of the nicotine is present in the free form but that the remaining 20% is bound to albumin and the phospholipids of the serum lipoproteins, the affinity for the drug increasing in the order albumins > HDL (High Density Lipoproteins) > LDL (Low Density Lipoproteins) > VLDL (Very Low Density Lipoproteins).

Stalhandske (1970) injected male albino mice intraperitoneally or intravenously with ^{14}C-nicotine and studied the distribution by taking whole body slices of the animals. One minute after the injection, the ratio between the concentrations in the brain and the blood was 5.6:1. They also found accumulation of the drug in the adrenal medulla, parotid glands and stomach. Similar findings, with only slight differences, were reported by Tsujimoto *et al.* (1975) [illegible] mined the [illegible] but[illegible]n of the drug in higher animals (dog and rhe[illegible]

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Several authors ha[illegible] [illegible]ibution of nicotine at a cellular level. Wadell and Marlowe (1975, 19[illegible] 197[illegible] found that the alkaloid was accumulated in the nonciliated epithelial cells of mouse bronchial tissue and bound strongly to melanin. The binding seemed to involve a reaction in which the nicotine was demethylated. These findings, particularly the strong affinity of nicotine for melanin-containing tissues, have been confirmed by Szuts *et al.* (1978).

Leeds and Turner (1977) found that nicotine was present, predominantly, in the microsomal fraction of cat and liver whereas in the pigeon it was located in the cytosol.

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5.2. Metabolism

5.2.1. *Sites of Nicotine Detoxification*

The systematic quantitative investigation of the route of nicotine detoxification began with the work of Werle (1938). The results, and the subsequent observations of other workers, have been summarized by Schievelbein (1968) and have all shown the liver to be the principal site for nicotine detoxification.

5.2.2. *Nature of Detoxification Process*

Werle and Uschold (1948) reported that the enzymic system which degrades nicotine requires oxygen, is inhibited by HCN and is bound to cell membranes. Hucker *et al.* (1960) have subsequently described a nicotine degradation system which requires microsomes, NADP, glucose-6-phosphate and an enzyme which is present in the supernatant fraction of ultracentrifuged liver homogenate.

5.2.3. *Factors Influencing the Metabolism of Nicotine*

Animal studies suggest that chronic nicotine administration does not enhance its metabolism (Takeuchi *et al.*, 1954; Werle and Mueller, 1941; Werle and Uschold, 1948) although Beckett and Triggs (1967) have observed that nicotine metabolism is increased in smokers when compared with nonsmokers. Hepatotoxic substances, such as ethanol, seem to decrease the ability of the liver to metabolize the alkaloid.

Nicotine detoxification is age dependent. For example, guinea-pigs in middle life are able to metabolize the drug faster than both young and old animals (Werle *et al.*, 1956). This has also been shown for mice (Stalhandske *et al.*, 1969) although the LD_{50} for nicotine in young mice was very similar to that found in adult animals inspite of the fact that the former metabolized the drug more slowly. Age also seems to be a factor in nicotine metabolism in humans since Klein and Gorrod (1978) have reported that, in both sexes, the amount of cotinine, in relation to nicotine-1′-*N*-oxide, excreted by older smokers was less than that excreted by the younger ones.

Nicotine metabolizing activity is enhanced in liver microsome fractions prepared from animals treated with 2-acetoaminofluorene, benzo(a)pyrene (Yamamoto *et al.*, 1966) and phenobarbital (Both and Boyland, 1967). Lobeline inhibits the enzymatic degradation of nicotine by guinea-pig liver slices and observation which may be related to the cross tachyphylaxis between nicotine and lobeline although this has not been established with certainty (Schievelbein and Werle, 1962b).

5.3. Nature of the Products of Nicotine Metabolism

Since the early investigations, discussed in the introduction, much effort has gone into establishing the products of nicotine metabolism. This review will consider only the current views on the nature of nicotine metabolism in mammals. For detail reviews of earlier studies, the reader is referred to other works (Larson *et al.*, 1957; Larson and Silvette, 1968; McKennis, 1965).

The metabolic pathways for nicotine, currently accepted, are summarized in Fig. 4. Cotinine appears to be the major metabolite in most species including man (Bowman *et al.*, 1959), its formation involving at least two enzyme systems. 5′-Hydroxynicotine and nicotine-Δ-1′ (5′)-iminium ion have been identified as intermediates in its metabolism (Murphy, 1973) and demethylcotinine has been shown to be formed from nornicotine (Papadopoulos, 1964; Wada *et al.*, 1961). Demethylation of both nicotine and cotinine has been reported to occur in the pig (Harke *et al.*, 1974).

Cotinine metabolism seems to involve hydroxylation of the pyrrolidine ring since 4-hydroxycotinine has been found in the urine of smokers (Bowman *et al.*, 1959) and in the urine of humans receiving cotinine (Bowman and McKennis, 1962).

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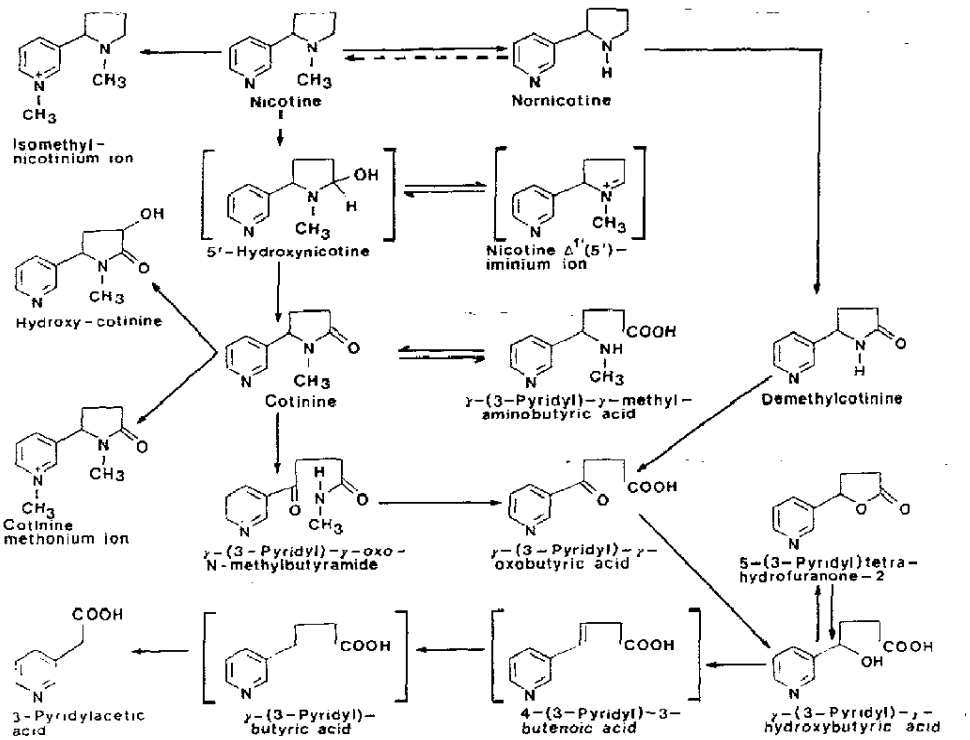

FIG. 4. Pathways of nicotine metabolism of nicotine in mammals. Proposed intermediates in brackets; broken arrows indicate supposed, but not confirmed, routes of metabolism (after Gorrod and Jenner, 1975).

All the other metabolites of nicotine, shown in Fig. 4 seem to arise by cleavage of the pyrrolidine ring of cotinine or demethylcotinine giving γ-(3-pyridyl)-γ-methylaminobutyric acid or γ-(3-pyridyl)-γ-oxo-*N*-methylbutyramide respectively (Hucker and Gillette, 1959). Both metabolites can be found in the urine of dogs receiving nicotine or cotinine and in the urine of smokers (Bowman *et al.*, 1959; McKennis *et al.*, 1957, 1958, 1949, 1961; Morselli *et al.*, 1967). γ-(3-pyridyl-γ-methylaminobutyric acid does not appear to be metabolized further whereas γ-(3-pyridyl)-γ-oxo-*N*-methylbutyramide undergoes further degradation to form γ-(3-pyridyl)-γ-oxo butyric acid, apparently by oxidative deamination. The compound is then metabolized to γ-(3-pyridyl)-γ-hydroxybutyric acid (McKennis *et al.*, 1964a,b; Turnbull *et al.*, 1958). This molecule can form the lactone 5-(3-pyridyl) tetrahydrofuranone-2 (Bowman, 1968; McKennis, 1965) and, although this lactone has not been detected as a metabolite of nicotine. Following administration of the known or supposed nicotine metabolites to rats, γ-(3-pyridyl)γ-hydroxybutyric acid, γ-(3-pyridyl)-butyric acid and 3-pyridylacetic acid were found.

3-Pyridylacetic acid, which has also been found in man (McKennis *et al.*, 1964a), seems to be the final product of nicotine metabolism. Possible intermediates are 4-(3-pyridyl)-3-butenoic acid and γ-(3-pyridyl)-butyric acid (McKennis, 1964b).

Early investigators postulated that nicotine was metabolized to nicotinic acid, a compound closely related to nicotinamide, the vitamin which is a precursor of NAD. This conclusion was the result of the rather unspecific methods used in the early studies, notably the Koenig reaction which is positive for both compounds although this erroneous pathway for nicotine metabolism may still be found in some modern textbooks.

There is little evidence to suggest that the pathway by which nicotine is degraded in mammals can be reversed, although Axelrod (1962) has reported that nornicotine can be converted to nicotine in the rabbit and that *in vitro* studies suggest that *S*-adenosyl

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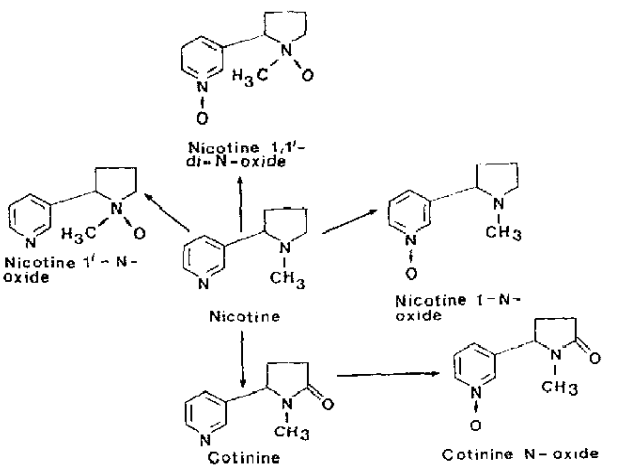

FIG. 5. Structures of *N*-oxidation products of nicotine (after Gorrod and Jenner, 1975).

methionine acted as the methyl group donor for the process. This observation was not confirmed by Morselli (1967).

The use of radioactively labelled nicotine permitted much greater progress in the evaluation of the products of nicotine metabolism. Using this approach, Papadopoulos and Kintzios (1963) were able to detect nicotine-1'-*N*-oxide in liver preparations incubated with labelled nicotine, an observation which was confirmed by Boyland and de Kock (1966) and Booth and Boyland (1967) who also showed that both enantiomeric forms of the molecule were present in the incubate. The amount of each isomer formed *in vitro* is dependent upon the species from which the liver is taken (Booth and Boyland, 1971). Nicotine-1'-*N*-oxide does not seem to be degraded further although, under anaerobic conditions, it is reported to be enzymically reduced back to nicotine. More recently, Booth and Boyland (1970) have shown that both stereoisomers of nicotine-1'-*N*-oxide are formed when liver tissue is incubated with (−)-nicotine *in vitro* and that the enzymes which catalyse these reactions appear to be stereospecific. Both the steroisomers have also been found in the urine of smokers. The formation of nicotine-1'-*N*-oxide seems to be a minor pathway of nicotine degradation and does not lead to the formation of any further metabolites.

The *N*-oxidation of cotinine has been reported to occur *in vivo* in monkeys although in this case, the nitrogen of the pyridine ring is oxidized (Dagne and Castagnoli, 1972). Direct *N*-methylation of the pyridine ring of nicotine has been reported in the dog (McKennis *et al.*, 1963) and the cotinine isomethonium ion has been found in the urine of dogs and humans given cotinine.

The *N*-oxidation of nicotine in man has been reviewed extensively by Gorrod and Jenner (1975) and the structures of the *N*-oxidized metabolites are summarized in Fig. 5. The biosynthesis and mammalian metabolism of nicotine has also been reviewed by Pilotti (1980), and the metabolism of other tobacco alkaloids has been reviewed by Gorrod and Jenner (1975).

5.4. Rate of Detoxification

Unfortunately, data on the rate of nicotine detoxification are very scarce. The early attempts which were made to estimate the detoxification time involved a comparison of the LD_{50} of nicotine in various species following the injection of the alkaloid at different time intervals (Larson *et al.*, 1949). The results, while allowing a comparison between the species, did not represent a measure of the maximum rate of detoxification of nicotine since the concentration of the alkaloid in the body built up gradually during the infusion.

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However, the results did show that the drug was detoxified quite rapidly by most animals but with considerable species variation.

Ganz *et al.* (1951) and Geiling (1951) found that, after an injection of ^{14}C-nicotine, the mouse eliminated almost all the radioactivity within 16 hr. In the dog, approximately 95% of a randomly labelled sample of nicotine administered intravenously as a dose of 1 or 10 mg/kg, appears in the urine within 36 hr (Bennett *et al.*, 1954). In these latter experiments, which seem to be the only reliable data for the dog, the excretion of total radioactivity, containing both nicotine and all its metabolites, was measured.

Additional information on the detoxification of nicotine can also be found in the following section.

6. EXCRETION

6.1. URINE

In cats, given a single dose of 40 μg of 2′-^{14}C-nicotine i.v., 55% of the radioactivity is excreted in the urine within 24 hr although only 1% is in the form of unchanged nicotine (Turner, 1969). These results are, to a large extent, consistent with earlier studies such as those of Hansson and Schmiterloew (1962) who found that 72.4% of a dose of ^{14}C-labelled nicotine injected into rats could be found in the urine collected over the 24 hr period following the injection.

In order to understand the nature of human smoking behavior in detail it would be valuable to relate the excretion of nicotine and its metabolites to the intake of nicotine in the tobacco smoke. This data, in combination with measurements of the plasma nicotine levels, could offer a means of estimating the amount of nicotine a nicotine-dependent smoker requires. We have tried to answer this question in some of our own studies. Volunteers smoked a certain brand of cigarette and the nicotine content of the butts was measured (Schulz and Seehofer, 1978). We found that the mean excretion of the nicotine contained in the cigarette smoke was 17.6% with a range of 9.6 to 38.8%. In Table 2 the absolute and relative amounts of excreted nicotine, cotinine and nicotine-1′-*N*-oxide are presented.

The rate of nicotine excretion is influenced by the pH of the urine (Beckett *et al.*, 1965; Schachter, 1978). Subjects, smoking 20 cigarettes per day at approximately regular intervals, excreted 0.1–4.3 (mean 1.0) μg nicotine/min when the urine was made acidic by the oral administration of ammonium chloride, and less than 0.1 μg nicotine/min when the urine was made alkaline by the oral administration of sodium bicarbonate. For the possible relevance of these results to humans smoking habits, see Schachter (1978).

Beckett and Triggs (1966) found that the rate of nicotine and cotinine excretion was not only influenced by the pH of the urine, but also by the rate of urine flow, an observation which has been confirmed in smokers by Feyerabend and Russell (1978).

Beckett and Triggs (1967) compared the recovery of nicotine from urine after the administration of nicotine by intravenous injection with that found following inhalation of the drug in the form of an aerosol. In male smokers they also examined the effect of

TABLE 2. *Mean Excretion of Nicotine and Metabolites Calculated as Nicotine in the 24 hr Urine of Smokers, who Smoked 20 Cigarettes Daily*

Smoker	Nicotine		Cotinine		Nicotine-1′-*N*-oxide	
	μg	%	μg	%	μg	%
Male $n = 75$	1042	33	1596	50	557	17
Female $n = 75$	1394	40	1502	43	585	17
Male + Female $n = 150$	1218	36	1549	46	571	17

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keeping the urine acidic. The study showed that, for each individual subject, the recovery of nicotine remained constant (±8%) but that the excretion of nicotine was greater in nonsmokers (55–70%) than smokers (25–50%). The authors concluded that habitual smoking induces the enzymatic metabolism of nicotine. However, since the excretion of cotinine was not increased in smokers, when compared with nonsmokers, it was also concluded that there is no significant induction of the pathway by which nicotine is metabolized to cotinine.

In a further study, Beckett *et al.* (1971) injected 3.07 mg of nicotine hydrogen tartrate, a dose which is equivalent to 1 mg of the free base, into male and female smokers and nonsmokers while maintaining an acid urine. The recoveries of nicotine and cotinine in the urine of one group of male smokers were lower than in the matched group of male nonsmokers. However, another group of smokers showed a similar recovery of nicotine but an increased recovery of cotinine when compared with nonsmokers. Female smokers excreted consistently less nicotine but more cotinine than female nonsmokers. The authors concluded that nicotine metabolism in humans is sex-dependent and that smoking causes alterations in its metabolism.

6.2. Feces

Fishman (1963) reported that, following an intraperitoneal injection of nicotine, randomly labelled with ^{14}C, into guinea-pigs, 2% of the radioactive label could be recovered in the feces collected over the subsequent 18 hr period. After the intravenous injection of radioactive nicotine into two dogs, the feces collected over the following 24 hr contained 2.5 and 7.2% respectively of the radioactivity.

The intravenous injection of 40 μg (approximately the dose of one puff) of ^{14}C-nicotine resulted in only 0.5% of the dose appearing in the first 24 hr sample of the feces (Turner, 1969).

6.3. Bile

In rats, 2.0–3.5% of injected ^{14}C-nicotine is found to be excreted into the bile in 6 hr. Autoradiograms of the bile showed that two radioactive compounds were present with the same R_f values as nicotine and cotine (Hansson and Schmiterloew, 1962). After the intravenous administration of ^{14}C-nicotine to cats, 0.5% of the radioactivity was found in the bile collected over a 4 hr period (Turner, 1969).

6.4. Saliva

High concentrations of ^{14}C-nicotine were found in the salivary glands of mice following both the intramuscular and intravenous injection of labelled drug and it has been suggested that this may be a pathway for the excretion of the alkaloid (Hansson and Schmiterloew, 1962; Schmiterloew and Hansson, 1962). Immediately after the intravenous administration of ^{3}H-nicotine to dogs and rhesus monkeys, Tsujimoto *et al.* (1972) also found high concentrations of the drug in parotid and submandibular saliva induced by pilocarpine infusion. The excretory patterns in both glands were almost identical although there were differences between the two species studied. Nicotine seemed to be more readily secreted into saliva than its metabolites.

6.5. Gastric Juice

Autoradiograms taken 15 min after the injection of nicotine-methyl-^{14}C into mice showed that an appreciable amount of the drug was secreted into the stomach (Hansson and Schmiterloew, 1962). Even more activity was found in the stomach after 30 min.

Following the intravenous administration of 40 μg 2′-^{14}C-nicotine into cats, it was found that approximately 5% of the radioactivity could be recovered from the gastric

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juice collected over a 2 hr period (Turner, 1969). Unchanged nicotine represented 56.8% of this activity while 18.7% was cotinine. After a series of intravenous injections of ^{14}C-nicotine imitating smoking (4 μg/kg every 60 sec for 20 min) the gastric juice contained, after 2 hr, significant amounts of radioactivity composed almost entirely of ^{14}C-nicotine and ^{14}C-cotinine (Turner, 1971).

6.6. Milk and Breast Fluid

Results from a number of laboratories have shown that the amount of nicotine present in the milk of female smokers ranges between 0 and 0.16 mg/ml (Emanuel, 1931; Nagy, 1934a,b; Perlmon *et al.*, 1942). More recently, Hill and Wynder (1979) have found both nicotine and cotinine in the breast fluid of five menstruating smokers. Thirty minutes after smoking cigarettes with a mean delivery of 0.75 mg nicotine and yielding a mean plasma level of 39 ng/ml nicotine and 369 ng/ml cotinine, the breast fluid contained mean concentrations of 40 ng/ml of nicotine and 169 ng/ml of cotinine.

7. CONCLUDING REMARKS

This review represents only a short extract of the great many publications covering the whole field of nicotine biochemistry and pharmacology and which are, in turn, only a small part of the overall theme 'smoking and health'. Inspite of the results reported by many others, we are not yet able to account for all the nicotine that smokers take in. This holds true for different brands of cigarettes and for different smoking behaviors. As a result it is not possible to establish what proportion of smokers smoke in order to dose themselves with nicotine and what proportion are smoking in order to receive other constituents of tobacco smoke or for whom it is habit with many underlying motivations.

Nicotine forms part of the smoke condensate and, in comparison with the many carcinogenic components of the condensate, is relatively harmless. Thus, it would seem sensible to increase the ratio between nicotine and the more hazardous materials although, in order to do this, it will be necesaary to determine the amount of nicotine that would have to be added to produce a satisfying smoke which minimizes the exposure to the more toxic components of the tobacco smoke. This information would be very valuable, and it is to be hoped that future studies will provide conclusive results in this regard. Such studies are in progress at the present time.

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